

EXHIBIT 6

**Amendment in Response to
November 3, 2008 Office Action**

Submitted: May 4, 2009

Serial No. 10/821,726

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Applicants: Michael Wayne Graham et al.

United States Court of Appeals,
 Federal Circuit.
 In re Mark A. VAECK, Wipa Chungjatupornchai
 and Lee McIntosh.
No. 91-1120.

Oct. 21, 1991.

Inventor sought patent for claimed invention directed to use of genetic engineering techniques for production of insecticidal proteins. The United States Patent and Trademark Office Board of Patent Appeals and Interferences affirmed an examiner's rejection of certain claims, and appeal was taken. The Court of Appeals, Rich, Circuit Judge, held that: (1) patent application was improperly rejected on ground of prima facie obviousness, and (2) patent application was properly rejected to extent that claims were too general to enable person skilled in art to make and use claimed invention without undue experimentation.

Affirmed in part, reversed in part.

Mayer, Circuit Judge, dissented and filed opinion.

West Headnotes

[1] Patents 291 ⚡ 314(5)

291 Patents

291XII Infringement

291XII(C) Suits in Equity

291k314 Hearing

291k314(5) k. Questions of Law or Fact. Most Cited Cases

Obviousness of invention for which patent is sought is legal question which court independently reviews, though based upon Patent and Trademark Office's underlying factual findings, which court reviews under clearly erroneous standard. 35 U.S.C.A. § 103.

[2] Patents 291 ⚡ 16(2)

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16 Invention and Obviousness in General

291k16(2) k. Prior Art in General.

Most Cited Cases

In reviewing rejection of invention for patent as obvious in view of combination of prior art references, court considers whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that in so making or carrying out, those of ordinary skill would have reasonable expectation of success; both suggestion and reasonable expectation of success must be found in prior art, not in applicant's disclosure. 35 U.S.C.A. § 103.

[3] Patents 291 ⚡ 16.25

291 Patents

291II Patentability

291II(A) Invention; Obviousness

291k16.25 k. Chemical Compounds. Most Cited Cases

Patent application for genetic engineering techniques for production of insecticidal proteins was improperly rejected on ground of prima facie obviousness; prior art did not disclose or suggest expression in cyanobacteria of chimeric gene encoding insecticidally active protein, or convey to those of ordinary skill reasonable expectation of success in doing so. 35 U.S.C.A. § 103.

[4] Patents 291 ⚡ 99

291 Patents

291IV Applications and Proceedings Thereon

291k99 k. Description of Invention in Specification. Most Cited Cases

To be patentable, specification of patent must enable any person skilled in art to which it pertains to

make and use claimed invention without undue experimentation. 35 U.S.C.A. § 112.

[5] Patents 291 ↪99

291 Patents

291IV Applications and Proceedings Thereon

291k99 k. Description of Invention in Specification. Most Cited Cases

Patent application for using genetic engineering techniques to produce insecticidal proteins was properly rejected to extent that claims were too general to enable person skilled in art to make and use claimed invention without undue experimentation; claim referred to use of cyanobacteria in general as host organism, despite fact that cyanobacteria were diverse and relatively poorly studied group of organisms, comprising some 150 different genera, with successful use of any one type in manner called for in invention being unpredictable. 35 U.S.C.A. § 112.

[6] Patents 291 ↪99

291 Patents

291IV Applications and Proceedings Thereon

291k99 k. Description of Invention in Specification. Most Cited Cases

Although patent applicants are not required to disclose every species encompassed by their claims, even in unpredictable art, in order to satisfy enablement requirement for patentability, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use invention as broadly as it is claimed. 35 U.S.C.A. § 112.

Patents 291 ↪328(2)

291 Patents

291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents

291k328 Patents Enumerated

291k328(2) k. Original Utility. Most Cited Cases
4,695,455. Cited.

***489** Ian C. McLeod, Ian C. McLeod, P.C., Okemos, Mich., argued for appellant.

Teddy S. Gron, Associate Sol., Office of the Sol., of Arlington, Va., argued for appellee. With him on the brief were Fred E. McKelvey, Sol. and Richard E. Schafer, Associate Sol.

Before RICH, ARCHER, and MAYER, Circuit Judges.

RICH, Circuit Judge.

This appeal is from the September 12, 1990 decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), affirming the examiner's rejection of claims 1-48 and 50-52 of application Serial No. 07/021,405, filed March 4, 1987, titled "Hybrid Genes Incorporating a DNA Fragment Containing a Gene Coding for an Insecticidal Protein, Plasmids, Transformed Cyanobacteria Expressing Such Protein and Method for Use as a Biocontrol Agent" as unpatentable under 35 U.S.C. § 103, as well as the rejection of claims 1-48 and 50-51 under 35 U.S.C. § 112, first paragraph, for lack of enablement. We reverse the § 103 rejection. The § 112 rejection is affirmed in part and reversed in part.

BACKGROUND

A. The Invention

The claimed invention is directed to the use of genetic engineering techniques ^{FN1} for production of proteins that are toxic to insects such as larvae of mosquitos and black flies. These swamp-dwelling pests are the source of numerous human health problems, including malaria. It is known that certain species of the naturally-occurring *Bacillus* genus of bacteria produce proteins ("endotoxins") that are toxic to these insects. Prior art methods of combatting the insects involved spreading or spraying crystalline spores of the insecticidal *Bacillus*

proteins over swamps. The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before being consumed, thus rendering this method prohibitively expensive. Hence the need for a lower-cost method of producing the insecticidal *Bacillus* proteins in high volume, with application in a more stable vehicle.

FN1. Basic vocabulary and techniques for gene cloning and expression have been described in *In re O'Farrell*, 853 F.2d 894, 895-99, 7 U.S.P.Q.2d 1673, 1674-77 (Fed.Cir.1988), and are not repeated here.

As described by appellants, the claimed subject matter meets this need by providing for the production of the insecticidal *Bacillus* proteins within host cyanobacteria. Although both cyanobacteria and bacteria are members of the procaryote^{FN2} kingdom, the cyanobacteria (which in the past have been referred to as "blue-green algae") are unique among procaryotes in that the cyanobacteria are capable of oxygenic photosynthesis. The cyanobacteria grow on top of swamps where they are consumed by mosquitos and black flies. Thus, when *Bacillus* proteins are produced within*490 transformed^{FN3} cyanobacterial hosts according to the claimed invention, the presence of the insecticide in the food of the targeted insects advantageously guarantees direct uptake by the insects.

FN2. All living cells can be classified into one of two broad groups, procaryotes and eucaryotes. The procaryotes comprise organisms formed of cells that do not have a distinct nucleus; their DNA floats throughout the cellular cytoplasm. In contrast, the cells of eucaryotic organisms such as man, other animals, plants, protozoa, algae and yeast have a distinct nucleus wherein their DNA resides.

FN3. "Transformed" cyanobacteria are those that have successfully taken up the foreign *Bacillus* DNA such that the DNA information has become a permanent part

of the host cyanobacteria, to be replicated as new cyanobacteria are generated.

More particularly, the subject matter of the application on appeal includes a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the *Bacillus* genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing^{FN4} the *Bacillus* gene in a host cyanobacterium, so as to produce the desired insecticidal protein.

FN4. "Expression" of a gene refers to the production of the protein which the gene encodes; more specifically, it is the process of transferring information from a gene (which consists of DNA) via messenger RNA to ribosomes where a specific protein is made.

The claims on appeal are 1-48 and 50-52, all claims remaining in the application. Claim 1 reads:

1. A chimeric gene capable of being expressed in Cyanobacteria cells comprising:
 - (a) a DNA fragment comprising a promoter region which is effective for expression of a DNA fragment in a Cyanobacterium; and
 - (b) at least one DNA fragment coding for an insecticidally active protein produced by a *Bacillus* strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein,

the DNA fragments being linked so that the gene is expressed.

Claims 2-15, which depend from claim 1, recite preferred *Bacillus* species, promoters, and selectable markers.^{FN5} Independent claim 16 and claims 17-31 which depend therefrom are directed to a hybrid plasmid vector which includes the chimeric gene of claim 1. Claim 32 recites a bacterial strain. Independent claim 33 and claims 34-48 which depend therefrom recite a cyanobacterium which ex-

presses the chimeric gene of claim 1. Claims 50-51 recite an insecticidal composition. Claim 52 recites a particular plasmid that appellants have deposited.

FN5. In the context of the claimed invention, "selectable markers" or "marker genes" refer to antibiotic-resistance conferring DNA fragments, attached to the gene being expressed, which facilitate the selection of successfully transformed cyanobacteria.

B. Appellants' Disclosure

In addition to describing the claimed invention in generic terms, appellants' specification discloses two particular species of *Bacillus* (*B. thuringiensis*, *B. sphaericus*) as sources of insecticidal protein; and nine genera of cyanobacteria (*Synechocystis*, *Anacystis*, *Synechococcus*, *Agmenellum*, *Aphanocapsa*, *Gloeocapsa*, *Nostoc*, *Anabaena* and *Fremyella*) as useful hosts.

The working examples relevant to the claims on appeal detail the transformation of a single strain of cyanobacteria, i.e., *Synechocystis* 6803. In one example, *Synechocystis* 6803 cells are transformed with a plasmid comprising (1) a gene encoding a particular insecticidal protein ("B.t. 8") from *Bacillus thuringiensis* var. *israelensis*, linked to (2) a particular promoter, the P_L promoter from the bacteriophage Lambda (a virus of *E. coli*). In another example, a different promoter, i.e., the *Synechocystis* 6803 promoter for the rubisco operon, is utilized instead of the Lambda P_L promoter.

C. The Prior Art

A total of eleven prior art references were cited and applied, in various combinations, against the claims on appeal.

The focus of Dzelzkalns,^{FN6} the primary reference cited against all of the rejected claims, is to determine whether chloroplast promoter sequences can

function in cyanobacteria. To that end Dzelzkalns discloses the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter*491 sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT).^{FN7} Importantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene; this use of antibiotic resistance-conferring genes for selection purposes is a common technique in genetic engineering.

FN6. 12 *Nucleic Acids Res.* 8917 (1984).

FN7. Chloramphenicol is an antibiotic; CAT is an enzyme which destroys chloramphenicol and thus imparts resistance thereto.

Sekar I,^{FN8} Sekar II,^{FN9} and Ganesan^{FN10} collectively disclose expression of genes encoding certain *Bacillus* insecticidal proteins in the bacterial hosts *B. megaterium*, *B. subtilis* and *E. coli*.

FN8. 137 *Biochem. and Biophys. Res. Comm.* 748 (1986).

FN9. 33 *Gene* 151 (1985).

FN10. 189 *Mol. Gen. Genet.* 181 (1983).

Friedberg^{FN11} discloses the transformation of the cyanobacterium *Anacystis nidulans* R2 by a plasmid vector comprising the O_LP_L operator-promoter region and a temperature-sensitive repressor gene of the bacteriophage Lambda. While the cyanobacteria are attractive organisms for the cloning of genes involved in photosynthesis, Friedberg states, problems may still be encountered such as suboptimal expression of the cloned gene, detrimental effects on cell growth of overexpressed, highly hydrophobic proteins, and rapid turnover of some gene products. To address these problems, Friedberg teaches the use of the disclosed Lambda regulatory signals in plasmid vehicles which, it states, have "considerable potential for use as vectors the expression of which can be controlled in *Anacystis*...."

FN11. 203 *Mol. Gen. Genet.* 505 (1986).

Miller^{FN12} compares the initiation specificities *in vitro* of DNA-dependent RNA polymerases^{FN13} purified from two different species of cyanobacteria (*Fremyella diplosiphon* and *Anacystis nidulans*), as well as from *E. coli*.

FN12. 140 *J. Bacteriology* 246 (1979).

FN13. RNA polymerase, the enzyme responsible for making RNA from DNA, binds at specific nucleotide sequences (promoters) in front of genes in DNA, and then moves through the gene making an RNA molecule that includes the information contained in the gene. Initiation specificity is the ability of the RNA polymerase to initiate this process specifically at a site(s) on the DNA template.

Nierzwicki-Bauer^{FN14} identifies in the cyanobacterium *Anabaena* 7120 the start site for transcription of the gene encoding *rbcL*, the large subunit of the enzyme ribulose-1,5-bisphosphate carboxylase. It reports that the nucleotide sequence 14-8 base pairs preceding the transcription start site "resembles a good *Escherichia coli* promoter," but that the sequence 35 base pairs before the start site does not.

FN14. 81 *Proc. Natl. Acad. Sci. USA* 5961 (1984).

Chauvat^{FN15} discloses host-vector systems for gene cloning in the cyanobacterium *Synechocystis* 6803, in which the antibiotic resistance-conferring *neo* gene is utilized as a selectable marker.

FN15. 204 *Mol. Gen. Genet.* 185 (1986).

Reiss^{FN16} studies expression in *E. coli* of various proteins formed by fusion of certain foreign DNA sequences with the *neo* gene.

FN16. 30 *Gene* 211 (1984).

Kolowsky^{FN17} discloses chimeric plasmids designed for transformation of the cyanobacterium *Synechococcus* R2, comprising an antibiotic-resistant gene linked to chromosomal DNA from the *Synechococcus* cyanobacterium.

FN17. 27 *Gene* 289 (1984).

Barnes, United States Patent No. 4,695,455, is directed to the treatment with stabilizing chemical reagents of pesticides produced by expression of heterologous genes (such as those encoding *Bacillus* proteins) in host microbial cells such as *Pseudomonas* bacteria. The host cells are killed by this treatment, but the resulting pesticidal compositions exhibit prolonged toxic activity when exposed to the environment of target pests.

*492 D. The Grounds of Rejection

1. The § 103 Rejections

Claims 1-6, 16-21, 33-38, 47-48 and 52 (which include all independent claims in the application) were rejected as unpatentable under 35 U.S.C. § 103 based upon Dzelzkalns in view of Sekar I or Sekar II and Ganesan. The examiner stated that Dzelzkalns discloses a chimeric gene capable of being highly expressed in a cyanobacterium, said gene comprising a promoter region effective for expression in a cyanobacterium operably linked to a structural gene encoding CAT. The examiner acknowledged that the chimeric gene and transformed host of Dzelzkalns differ from the claimed invention in that the former's structural gene encodes CAT rather than insecticidally active protein. However, the examiner pointed out, Sekar I, Sekar II, and Ganesan teach genes encoding insecticidally active proteins produced by *Bacillus*, and the advantages of expressing such genes in heterologous^{FN18} hosts to obtain larger quantities of the protein. The examiner contended that it would have been obvious to one of ordinary skill in the art to substitute the *Bacillus* genes taught by Sekar I, Sekar II, and Ganesan for the CAT gene in the vec-

tors of Dzelzkalns in order to obtain high level expression of the *Bacillus* genes in the transformed cyanobacteria. The examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes. In the absence of evidence to the contrary, the examiner contended, the invention as a whole was prima facie obvious.

FN18. Denotes different species or organism.

Additional rejections were entered against various groups of dependent claims which we need not address here. All additional rejections were made in view of Dzelzkalns in combination with Sekar I, Sekar II, and Ganesan, and further in view of other references discussed in Part C above.

The Board affirmed the § 103 rejections, basically adopting the examiner's Answer as its opinion while adding a few comments. The legal conclusion of obviousness does not require absolute certainty, the Board added, but only a reasonable expectation of success, citing *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed.Cir.1988). In view of the disclosures of the prior art, the Board concluded, one of ordinary skill in the art would have been motivated by a reasonable expectation of success to make the substitution suggested by the examiner.

2. The § 112 Rejection

The examiner also rejected claims 1-48 and 50-51 under 35 U.S.C. § 112, first paragraph, on the ground that the disclosure was enabling only for claims limited in accordance with the specification as filed. Citing *Manual of Patent Examining Procedure* (MPEP) provisions 706.03(n) ^{FN19} and (z) ^{FN20} as support, the examiner took the position that undue experimentation would be required of the art worker to practice the claimed invention, in view of the unpredictability in the art, the breadth

of the claims, the limited number of working examples and the limited guidance provided *493 in the specification. With respect to unpredictability, the examiner stated that

FN19. MPEP 706.03(n), "Correspondence of Claim and Disclosure," provides in part:

In chemical cases, a claim may be so broad as to not be supported by [the] disclosure, in which case it is rejected as unwarranted by the disclosure....

FN20. MPEP 706.03(z), "Undue Breadth," provides in part:

[I]n applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Sol*, 1938 C.D. 723; 497 O.G. 546. This is because in arts such as chemistry it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 1940 C.D. 351; 518 O.G. 255 gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." ...

[t]he cyanobacteria comprise a large and diverse group of photosynthetic bacteria including large numbers of species in some 150 different genera including *Synechocystis*, *Anacystis*, *Synechococcus*, *Agmenellum*, *Nostoc*, *Anabaena*, etc. The molecular biology of these organisms has only recently become the subject of intensive investigation and this work is limited to a few genera.

Therefore the level of unpredictability regarding heterologous gene expression in this large, diverse and relatively poorly studied group of procaryotes is high....

The Board affirmed, noting that "the limited guidance in the specification, considered in light of the relatively high degree of unpredictability in this particular art, would not have enabled one having ordinary skill in the art to practice the broad scope of the claimed invention without undue experimentation. *In re Fisher*, 427 F.2d 833, 166 U.S.P.Q. 18 (CCPA 1970)."

OPINION

A. Obviousness

[1] We first address whether the PTO erred in rejecting the claims on appeal as prima facie obvious within the meaning of 35 U.S.C. § 103. Obviousness is a legal question which this court independently reviews, though based upon underlying factual findings which we review under the clearly erroneous standard. *In re Woodruff*, 919 F.2d 1575, 1577, 16 U.S.P.Q.2d 1934, 1935 (Fed.Cir.1990).

[2] Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir.1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

[3] We agree with appellants that the PTO has not

established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding *Bacillus* insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The PTO argues that the substitution of insecticidal *Bacillus* genes for CAT marker genes in cyanobacteria is suggested by the secondary references Sekar I, Sekar II, and Ganesan, which collectively disclose expression of genes encoding *Bacillus* insecticidal proteins in two species of host *Bacillus* bacteria (*B. megaterium* and *B. subtilis*) as well as in the bacterium *E. coli*. While these references disclose expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere do these references disclose or suggest expression of such genes in transformed cyanobacterial hosts.

To remedy this deficiency, the PTO emphasizes similarity between bacteria and cyanobacteria, namely, that these are both procaryotic organisms, and argues that this fact would suggest to those of ordinary skill the use of cyanobacteria as hosts for expression of the claimed chimeric genes. While it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends.*494 As the PTO concedes, cyanobacteria and bacteria are not identical; they are classified as two separate divisions of the kingdom Procaryotae.^{FN21} Moreover, it is only in recent years that the biology of cyanobacteria has been clarified, as evidenced by references in the prior art

to "blue-green algae." Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene.

FN21. *Stedman's Medical Dictionary* 1139 (24th ed. 1982) (definition of "Procaryotae"). Procaryotic organisms are commonly classified according to the following taxonomic hierarchy: Kingdom; Division; Class; Order; Family; Genus; Species. 3 *Bergey's Manual of Systematic Bacteriology* 1601 (1989).

At oral argument the PTO referred to additional secondary references, not cited against any independent claim (i.e., Friedberg, Miller, and Nierzwicki-Bauer), which it contended disclose certain amino acid sequence homology between bacteria and cyanobacteria. The PTO argued that such homology is a further suggestion to one of ordinary skill to attempt the claimed invention. We disagree. As with the Dzelzkalns, Sekar I, Sekar II, and Ganesan references discussed above, none of these additional references disclose or suggest that cyanobacteria could serve as hosts for expression of genes encoding *Bacillus* insecticidal proteins. In fact, these additional references suggest as much about *differences* between cyanobacteria and bacteria as they do about similarities. For example, Nierzwicki-Bauer reports that a certain nucleotide sequence (i.e., the -10 consensus sequence) in a particular cyanobacterium resembles an *E. coli* promoter, but that another nearby nucleotide sequence (the -35 region) does not. While Miller speaks of certain promoters of the bacteriophage Lambda that are recognized by both cyanobacterial and *E. coli* RNA polymerases, it also discloses that these promoters exhibited differing strengths when exposed to the different polymerases. Differing sensitivities of the respective polymerases to an inhibitor are also disclosed, suggesting differences in the structures of the initiation complexes.

The PTO asks us to agree that the prior art would lead those of ordinary skill to conclude that cyanobacteria are attractive hosts for expression of any and all heterologous genes. Again, we can not. The relevant prior art does indicate that cyanobacteria are attractive hosts for expression of both native and heterologous *genes involved in photosynthesis* (not surprisingly, for the capability of undergoing oxygenic photosynthesis is what makes the cyanobacteria unique among procaryotes). However, these references do not suggest that cyanobacteria would be equally attractive hosts for expression of *unrelated* heterologous genes, such as the claimed genes encoding *Bacillus* insecticidal proteins.

In *O'Farrell*, this court affirmed an obviousness rejection of a claim to a method for producing a "predetermined protein in a stable form" in a transformed bacterial host. 853 F.2d at 895, 7 U.S.P.Q.2d at 1674. The cited references included a prior art publication (the Polisky reference) whose three authors included two of the three coinventor-appellants. The main difference between the prior art and the claim at issue was that in Polisky, the heterologous gene was a gene for ribosomal RNA, while the claimed invention substituted a gene coding for a predetermined protein. *Id.* at 901, 7 U.S.P.Q.2d at 1679. Although, as the appellants therein pointed out, the ribosomal RNA gene is not normally translated into protein, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein, and further predicted that if a gene coding for a protein were to be substituted, extensive translation might result. *Id.* We thus affirmed, explaining that

the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the [claimed] method could be used to make proteins.

....

*495 ... Polisky contained detailed enabling

methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.

Id. at 901-02, 7 U.S.P.Q.2d at 1679-80.

In contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art. Moreover, the "reasonable expectation of success" that was present in *O'Farrell* is not present here. Accordingly, we reverse the § 103 rejections.

B. Enablement

[4] The first paragraph of 35 U.S.C. § 112 requires, *inter alia*, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed.Cir.1988). That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *Id.* at 736-37, 8 U.S.P.Q.2d at 1404. Enablement, like obviousness, is a question of law which we independently review, although based upon underlying factual findings which we review for clear error. *See id.* at 735, 8 U.S.P.Q.2d at 1402.

[5] In response to the § 112 rejection, appellants assert that their invention is "pioneering," and that this should entitle them to claims of broad scope. Narrower claims would provide no real protection, appellants argue, because the level of skill in this art is so high, art workers could easily avoid the claims. Given the disclosure in their specification, appellants contend that any skilled microbiologist could construct vectors and transform many different cyanobacteria, using a variety of promoters and *Bacillus* DNA, and could easily determine whether

or not the active *Bacillus* protein was successfully expressed by the cyanobacteria.

The PTO made no finding on whether the claimed invention is indeed "pioneering," and we need not address the issue here. With the exception of claims 47 and 48, the claims rejected under § 112 are not limited to any particular genus or species of cyanobacteria. The PTO's position is that the cyanobacteria are a diverse and relatively poorly studied group of organisms, comprising some 150 different genera, and that heterologous gene expression in cyanobacteria is "unpredictable." Appellants have not effectively disputed these assertions. Moreover, we note that only one particular species of cyanobacteria is employed in the working examples of appellants' specification, and only nine genera of cyanobacteria are mentioned in the entire document.

Taking into account the relatively incomplete understanding of the biology of cyanobacteria as of appellants' filing date, as well as the limited disclosure by appellants of particular cyanobacterial genera operative in the claimed invention, we are not persuaded that the PTO erred in rejecting claims 1-46 and 50-51 under § 112, first paragraph. There is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria. *See In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970) (the first paragraph of § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification).^{FN22} Accordingly, *496 we affirm the § 112 rejection as to those claims.

FN22. The enablement rejection in this case was not based upon a post-filing date state of the art, as in *In re Hogan*, 559 F.2d 595, 605-07, 194 U.S.P.Q. 527, 536-38 (CCPA 1977). *See also United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251, 9 U.S.P.Q.2d 1461, 1464

(Fed.Cir.1989) (citing *Hogan*); *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1568-69, 15 U.S.P.Q.2d 1039, 1047-48 (Fed.Cir.1990) (directing district court, on remand, to consider effect of *Hogan* and *United States Steel* on the enablement analysis of *Fisher*), *cert. dismissed*, 499 U.S. 955, 111 S.Ct. 1434, 113 L.Ed.2d 485 (1991). We therefore do not consider the effect of *Hogan* and its progeny on *Fisher's* analysis of when an inventor should be allowed to "dominate the future patentable inventions of others." *Fisher*, 427 F.2d at 839, 166 U.S.P.Q. at 24.

[6] In so doing we do *not* imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (CCPA 1976). However, there must be sufficient disclosure, either through illustrative examples or terminology,^{FN23} to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element. See *Fisher*, 427 F.2d at 839, 166 U.S.P.Q. at 24. In this case, we agree with the PTO that appellants' limited disclosure does not enable one of ordinary skill to make and use the invention as now recited in claims 1-46 and 50-51 without undue experimentation.

FN23. The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is irrelevant. *Id.*

Remaining dependent claim 47 recites a cyanobacterium which expresses the chimeric gene of claim 1, wherein the cyanobacterium is selected from among the genera *Anacystis* and *Synechocystis*. Claim 48, which depends from claim 47, is limited to the cyanobacterium *Synechocystis* 6803. The PTO did not separately address these claims, nor indicate why they should be treated in the same manner as the claims encompassing all types of cyanobacteria. Although these claims are not limited to expression of genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects. The rejection of claims 47-48 under § 112 will not be sustained.

CONCLUSION

The rejection of claims 1-48 and 50-52 under 35 U.S.C. § 103 is *reversed*. The rejection of claims 1-46 and 50-51 under 35 U.S.C. § 112, first paragraph, is *affirmed* and the rejection of claims 47 and 48 thereunder is *reversed*.

AFFIRMED-IN-PART, REVERSED-IN-PART.

MAYER, Circuit Judge, dissenting.

An appeal is not a second opportunity to try a case or prosecute a patent application, and we should not allow parties to "undertake to retry the entire case on appeal." *Perini America, Inc. v. Paper Converting Machine Co.*, 832 F.2d 581, 584, 4 U.S.P.Q.2d 1621, 1624 (Fed.Cir.1987); *Eaton Corp. v. Appliance Valves Corp.*, 790 F.2d 874, 877, 229 U.S.P.Q. 668, 671 (Fed.Cir.1986). But that is precisely what the court has permitted here. The PTO

conducted a thorough examination of the prior art surrounding this patent application and concluded the claims would have been obvious. The board's decision based on the examiner's answer which comprehensively explains the rejection is persuasive and shows how the evidence supports the legal conclusion that the claims would have been obvious. Yet, the court ignores all this and conducts its own examination, if you will, as though the examiner and board did not exist. Even if I thought this opinion were more persuasive than the board's, I could *497 not join it because it misperceives the role of the court.

The scope and content of the prior art, the similarity between the prior art and the claims, the level of ordinary skill in the art, and what the prior art teaches are all questions of fact. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 693-94, 15 L.Ed.2d 545, 148 U.S.P.Q. 459, 467 (1966); *Jurgens v. McKasy*, 927 F.2d 1552, 1560, 18 U.S.P.Q.2d 1031, 1037 (Fed.Cir.1991). And "[w]here there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous." *Anderson v. City of Bessemer City*, 470 U.S. 564, 574, 105 S.Ct. 1504, 1511-12, 84 L.Ed.2d 518 (1985). The mere denomination of obviousness as a question of law does not give the court license to decide the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous. *In re Woodruff*, 919 F.2d 1575, 1577, 16 U.S.P.Q.2d 1934, 1935 (Fed.Cir.1990); *In re Kulling*, 897 F.2d 1147, 1149, 14 U.S.P.Q.2d 1056, 1057 (Fed.Cir.1990). There may be more than one way to look at the prior art, but on this record we are bound by the PTO's interpretation of the evidence because it is not clearly erroneous and its conclusion is unassailable. I would affirm on that basis.

C.A.Fed.,1991.
In re Vaeck
947 F.2d 488, 20 U.S.P.Q.2d 1438

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